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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,552	06/21/2001	Michael W. Leviten	R-67	5854

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,552	LEVITEN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *1-7,9 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 11-8-04 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 17 has been added. Claims 1-17 are pending.

Election/Restrictions

This application contains claims 1-7, 9 and 11-16 drawn to an invention nonelected with traverse in the reply filed on 11-13-02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 8, 10 and 17 are under consideration.

Claim Rejections - 35 USC § 101

Claims 8 and 10 remain rejected and claim 17 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility for reasons of record.

> REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS repeated from http://www.uspto.gov/web/menu/utility.pdf
>
> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.
>
> "Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably

confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

(Page 5-7 of utility guidelines).

A "well-known utility" is a specific, substantial and credible utility which is well know, immediately apparent, or implied by the specification's disclosure of the properties of the material, alone or taken with the knowledge of one skilled in the art. Neither a "well-established utility" nor a "specific utility" applies to any utility that one can dream up for an invention or a utility that would apply to virtually every member of a general class of materials, such as proteins or DNA.

(Paragraph bridging pg 32-33 of utility guidelines).

Claims 8 and 17 are directed toward a transgenic mouse whose genome comprises a null cerberus (Cer1) allele, wherein the allele has the nucleic acid sequence of SEQ ID NO:1, wherein said mouse exhibits increased anxiety as compared to a wild-type mouse.

The specification teaches making the mice (pg 51, lines 1-6). Two homozygous mice were tested in an open field test (pg 51, lines 9-14; pg 52, Table 1). Applicants conclude that increased number of fecal boli during the ten-minute test indicated the mice had increase anxiety.

The mice claimed and described in the open field test study do not have a specific or substantial utility. It is not readily apparent that the results are statistically significant because only two knockout mice were tested. The results of the open field test merely indicate the mice defecated more frequently. It cannot be concluded that increased defecation is a sign of anxiety and not some muscular or gastrointestinal dysfunction. Significant "further experimentation" would be required to use the results of the open field test to determine the function of the cerberus gene. As such, mice with a disruption in the cerberus gene comprising SEQ ID NO:1, that defecate more frequently than a wild-type mouse in an open field test does not have utility as a model for anxiety.

The specification suggests using the mice as a model of disease, specifically as a model for neurological phenotypes (pg 17, line 30). The mice claimed do not have utility as a model of disease. The specification does not correlate any disease in humans to increased anxiety as claimed. The specification does not correlate increased anxiety found in humans to a disruption in a cerberus gene. Therefore, using the mice as a model of disease is not a specific or substantial utility.

The specification suggests using the mice to identify agents that ameliorate a phenotype (pg 18, line 8). Using the mice to identify agents capable of altering a phenotype would require further research and is not a

"substantial utility" or "specific utility" because the mouse may not be capable of identifying agents capable of treating disease. Bowery (Pharm. Rev., 2002, Vol. 54, pg 247-264) taught,

> "no unique pharmacological or functional properties have been assigned to either subunit or the variants" of $GABA_B$. "The emergence of high-affinity antagonists for $GABA_B$ receptors has enabled a synaptic role to be established. However, than antagonists have generally failed to establish the existence of pharmacologically distinct receptor types within the $GABA_B$ receptor class. The advent of $GABA_{B1}$ knockout mice has also failed to provide support for multiple receptor types" (pg 247, col. 2, line 4 on).

Thus, knockout mice may be used to identify agents that bind to the knocked out gene ($GABA_B$ in the case of Bowery or GPCR-like protein in the instant application), but the agent may not treat disease or ameliorate any symptom of disease. Further research would be required to determine how to use such an agent identified using the mouse, which is not a "substantial utility" (see Utility Guidelines for examples of things that do not have "substantial utility" "C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility"). Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be affecting other proteins in the pathway and not the cerberus protein itself. Using the mice to identify agents capable of altering a phenotype is also not a "specific utility" because the agent may be found using wild-type mice. Furthermore, the specification does not identify any such agents using the mice. Therefore, using

the mice to identify agents that alter the increased sensitivity to pain is not a specific, substantial or credible utility.

The specification suggests using the mice to identify agents that affect cerberus function (pg 18, lines 30-31). The mouse claimed cannot be used to identify agents that act on cerberus because the mice do not express cerberus.

It was "well-known" in the scientific community at the time of filing to knock out a gene in a mouse in an attempt to determine its function; however, it was also "well-known" that the mouse may only provide clues to the function of the gene and that the mouse may not be capable of determining the function of the gene. While the mouse may have "scientific utility," "scientific utility" is not the same as "patentable utility" or a "well-established" utility.

The utility guidelines specifically state that further research is not a "substantial utility":

> [T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of applicants' invention (with decreased anxiety or increased pain threshold) as a model of disease. Further study would be required to determine the function of the disrupted gene. The overall phenotype

of the applicants' mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder. Thus, using the mice claimed for further research is not a "substantial utility."

Using the mice to identify the function of the knocked out gene is not a "substantial utility" or "specific utility" because the phenotype may be caused by other proteins compensating for the deleted gene. Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). Thus, knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype may be a result of other compensating proteins and not the knocked out gene.

The function of a gene may not be found by studying a knockout mouse. Mombereau (Neuropsychopharmacology, 2004, Vol. 29, pg 1050-1062) used knockout mice that had increased anxiety further study to determine the function of $GABA_B$

receptor. Mombereau did not teach how to use mice with decreased anxiety as claimed. In addition, Mombereau did not determine the function of the $GABA_B$ receptor. Mombereau administered compounds known to antagonize $GABA_B$ receptor (found in *in vitro* assays, not in the mice) to the mice. Mombereau concluded that the mice merely confirmed $GABA_B$ was involved in a molecular pathway relevant for the manifestation of anxiety or depression. Mombereau did not determine the function of $GABA_B$ receptor using the $GABA_B$ -/- mice. Mombereau concludes "we acknowledge both the inherent difficulties and the caution needed in the interpretation of behavioral analysis of genetically modified mice such as the $GABA_B(1)$ -/- mice, which have overt behavioral disturbances, in more defined tests relevant to psychopathology. Nonetheless, the current data show that even such mice can still be utilized to give important indicators of the role of a given protein, in this case the $GABA_B$ receptor, in a molecular pathway relevant for the manifestation of anxiety or depression. These assertions can then be confirmed more parametrically using appropriate pharmacological activators and antagonists as we have done using novel $GABA_B$ receptor positive modulators and antagonists" (¶ bridging pg 1059-1060). Mombereau used the antagonists to confirm the "antidepressant-like phenotype of $GABA_B$ -/- mice pharmacologically (pg 1059, col. 1, 2nd full ¶, line 1-4). Therefore, using a mouse to merely obtain clues of the role of a protein in a molecular pathway of anxiety or to confirm the phenotype of the mouse pharmacologically as described by Mombereau is not a specific or substantial utility because it is generic to a pathway of anxiety and because it does not result in determining the function of the protein within the pathway.

Overall, the mice claimed do not have a "well-established utility" because using the mice for further research (to determine how to use the mouse as a model of non-disclosed disease, to determine the function of the gene or to identify agents capable of altering a phenotype) is not a "specific utility" or "substantial utility."

Claim 10, directed toward making a transgenic mouse, is included because the mouse being made does not have utility.

Applicants argue that one of skill would have recognized that the mouse has a well-established utility for defining the function and role of the disrupted gene, i.e. a tool in studying gene function (pg 8-11 of response filed 11-8-04). Applicants cite MPEP 2701 II(A)(3). Applicants cite an NIH report from 2004, Austin (Nature Genetics, 2004, Vol. 36, No. 9, pg 921-24), Genes VII (Lewin, Oxford University Press, 2000), Crawley (2000, What's wrong with my mouse, Behavioral phenotyping of transgenic and knockout mice, Wiley-Liss) and Crabbe (Science, 1999, Vol. 284, pg 1670-1672), which state knockout mice can be used to determine the function of genes. Applicants' arguments are not persuasive. MPEP 2701 II(A)(3) states:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible. (underlining added for emphasis)

In summary, the MPEP states a well-established utility must be specific, substantial and credible. In this case, using the mice to determine the function of the

cerberus gene rises merely to the level of a scientific utility, but does not rise to the level of a specific, substantial and credible utility. Significant further research would be required to determine the function of the cerberus gene by determining the expression analysis of the cerberus gene. The mice do not compare to "gas chromatographs, screening assays and nucleotide sequencing techniques" as argued on pg 10, last full paragraph, of the response filed 11-8-04, because the mice may not reveal the function of the cerberus gene. Using the mice to determining where the protein is expressed is not a substantial or specific utility in this case because the specification states cerberus is expressed "in most every tissue." Therefore, using the mice to determine the function of the cerberus gene is not a well-established utility because the function may not be determined.

Applicants argue the motivational statement in the 103 rejection shows that those of skill in the art at the time of filing wanted to disrupt genes in mice to determine the function of the genes (pg 11). Applicants' argument is not persuasive. Motivation to disrupt a gene in a mouse to determine the function of the genes clearly existed at the time of filing. The desire to determine the function of the gene does not negate the fact that the mouse may not provide the function of the gene. Obtaining a mouse with a disruption in a gene did not guarantee determining the function of the disrupted gene or obtaining a mouse that was a model of disease.

Applicants cite Lewejohann and Haller which are not evidence of utility because they were not available at the time of filing. Neither reference

determined the function of the knockout gene using the knockout mouse. In the case of Lewejohann, the researches merely conclude that BC1 contributed to the "aptive modulation of behaviour" [sic]. Lewejohann did not determine the function of BC1 or how BC1 modulated behaviour. The results were not specific to anxiety. In the case of Haller, antagonists of CB1 were required for the assays described by Haller. In the case of the instant invention, no modulators of cerberus were known at the time of filing. Significant further research would be required to isolate modulators of cerberus because the mice of applicants invention do not express cerberus and because compounds identified as altering a phenotype using the mice of applicants' invention may actually be modulating a protein in a pathway related to cerberus protein and not cerberus itself (see Olsen cited above who taught proteins in a pathway may compensate for the disrupted gene and cause the phenotype and that the phenotypes of mice with anxiety are generic to a pathway of proteins.

Applicants cite en re Brana and state the PTO has the initial burden of challenging the asserted utility in the disclosure (pg 14 of response). Applicants argue that contrary to the product in En re Brenner, whose sole 'utility' consisted of its potential role as an object of use-testing, the mouse claimed can be used to determine the function of SEQ ID NO:1. Applicants' arguments are not persuasive. *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992) indicated that a product known in the art did not necessarily have patentable utility. The examiner has challenged all of the asserted utilities in the disclosure and has

challenged what applicants consider "well-established" utilities. The mouse claimed might only provide a clue to a pathway in which SEQ ID NO:1 is involved. This is not a specific utility because results from the tests only indicate SEQ ID NO:1 is involved in a pathway relating to anxiety. The phenotype provides only a clue that SEQ ID NO:1 is generically involved in a pathway having a number of proteins. Using the mouse to determine the function of SEQ ID NO:1 is not credible or substantial because the function of SEQ ID NO:1 may never be found using the mouse. Assuming further study of the mouse will elucidate the function of SEQ ID NO:1, the amount of research required to do so would be significant. The specification does not guide those of skill in any particular direction so that one of skill could simply perform an assay to determine the function of SEQ ID NO:1.

Applicants cite Doetschman (Lab. Animal Sci. 1999, Vol. 49, pg 137-143), which taught knockout phenotypes provide accurate information concerning gene function (pg 16 of response. Applicants' argument is not persuasive. Doetschman taught that the phenotype may be caused by the mixed background of the knockout mice and not be caused by the knockout (¶ bridging pg 28-29). Doetschman does not teach that every mouse with a disruption will reveal the function of the disrupted gene. The knockout mice described by Doetschman merely provide clues as to the disrupted gene's function. Significant further investigation would be required to determine the function of a gene using any

mouse described by Doetschman. Therefore, Doetschman does not establish that any mouse with a disruption in any gene has a "well-established" utility.

Claim Rejections - 35 USC § 112

Enablement

Claims 8 and 10 remain rejected and claim 17 is rejected under 35 U.S.C. 112, first paragraph for reasons of record. The claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above; therefore, one skilled in the art clearly would not know how to use mice having a disruption in SEQ ID NO:1 as claimed.

Applicants' arguments to the enablement rejection are found in the arguments to the utility rejection, which have been addressed above in the utility rejection.

Indefiniteness

Claim 10 is newly rejected and new claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite because a "pseudopregnant mouse" does not give birth as claimed.

The phrase "anti-depressive" behavior is unclear in claim 17. It is unclear if the phrase means the mouse is coming out of a depression or if the phrase means the mouse is not depressed or if the phrase means the mouse is the opposite of depressed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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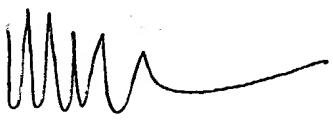
For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER